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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,502	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70 and 72-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70 and 72-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 1-69 and 71 have been cancelled. Claims 70 and 73 have been amended.

Claims 70 and 72-77 are pending and under examination.

Response to Arguments

Double Patenting

3. The nonstatutory obviousness-type double patenting rejections of claims 70 and 73-77 as being unpatentable over claims 7-13 and 16-18 of U.S. Patent No. 6,146,894, of claims 70 and 72-77 over claims 1, 3-7, and 12 of U.S. Patent No. 6,808,894, and of claims 70 and 72-77 over claims 1-3 and 6 of U.S. Patent No. 6,825,038 are withdrawn in response to Applicant's amendments to the claims to recite selecting cells comprising a mutation that results in enhanced immunogencity of the preselected immunogen. The amendments were filed on 03/19/2007.

However, similar rejections are made below citing prior art evidencing that mutations can result in enhanced antigen immunogenicity.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. Claim 70 and 72-77 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the reasons of record set forth in the non-final Office action mailed on 12/18/2006. Applicant's arguments filed 03/19/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that once a cell comprising a mutation in the gene of interest is selected, one of skill in the art could stabilize the cell comprising the mutation and express the gene or one of skill in the art could isolate the mutated gene and express it in a genetically stable cell. Applicant argues that the particular expression system is not critical and that the claim inherently contains the link between the selection and expression steps. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, this appears to be inconsistent with the cell having PMS2 in it, since it introduces genetic mutations. Review of the specification fails to provide any guidance to what is encompassed by this limitation. More clearly setting forth the basis or nature of what is genetically stable or how this limitation is obtained would address the basis of the rejection.

Claims 72-77 are rejected for being dependent from the rejected claim 70 and also for failing to further clarify the basis of the rejection.

Claim Rejections - 35 USC § 112, written description

5. Claims 70, 72, 73, 76, and 77 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons

of record set forth in the non-final Office action mailed on 12/18/2006. Applicant's arguments filed 03/19/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the claims are drawn to methods using a dominant negative PMS2 and that several species of dominant negative PMS2 of various origin can be employed ant that these species have been described in the specification, which species constitute a substantial portion of the claimed genus. Applicant argues that one of skill in the art would be capable of identifying PMS2 genes in a cell and also of identifying dominant negative variants of PMS2. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant's argument that the specification describes a substantial portion of the claimed genus is not found persuasive because the specification only discloses the dominant negative mutant of the human PMS2, i.e., hPMS2-134, which carries a truncating mutation at codon 134; the specification further indicates that other dominant negative mutants can be identified from cells of different species organisms, such as humans, animals, yeast, or bacteria, by screening the cells for defective mismatch repair or that such mutants can be artificially created by producing variants of hPMS2-134 (p. 9, lines 13-19, p. 10, lines 1-5). It is clear from the specification that Applicant was, at the time of filing, in possession of only one species of the broad claimed genus (i.e., hPMS2-134) and that the specification did not disclose a substantial portion of the genus, as Applicant argues, because the species mentioned by the Applicant were, at

the time the invention was made, yet to be discovered. One of skill in the art would readily recognize that Applicant was not in possession of the claimed genus at the time of filing. Even the fact that one of skill in the art would be capable of identifying the above species indicates that Applicant was not in possession of the entire genus. In fact, Applicant was only in possession of hPMS2-134. For these reasons, and for the reasons set forth in the non-final Office action mailed on 12/18/2006, the rejection is maintained.

It is noted that claims 74 and 75 are directly or indirectly dependent from the rejected claims 70, 72, and 73.

Claim Rejections - 35 USC § 112, enablement

6. Claims 70, 72, 73, 76, and 77 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record set forth in the non-final Office action mailed on 12/18/2006. Applicant's arguments filed 03/19/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Applicant needs not enable every mode of making and using the invention and that the enablement requirement is fulfilled if any mode of making and using the invention is enabled. Applicant argues that, as amended, the claims are directed to methods using a dominant negative PMS2 and that several species of dominant negative PMS2 of widely divergent species are disclosed in the specification and that the specification also provides detailed guidance for assessing defective mismatch repair (Example 1) and

therefore, multiple modes to practice the claimed invention have been provided. Applicant submits that it is within the skill in the art to assay for defects in MMR activity in a given cell (Example 3 and 4) and that it is just routine, and not undue, experimentation to screen candidate dominant negative PMS2 mutants. Applicant continues arguing that, since the various structural and functional attributes of dominant negative PMS2 mutants are described in the specification and the art, the specification provides specific starting materials and the conditions under which the invention could be practiced. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant's argument that the specification discloses several species of dominant negative PMS2 of widely divergent species and that the specification also provides detailed guidance for assessing defective mismatch repair in a given cell is not found persuasive. The specification only discloses the dominant negative mutant of the human PMS2, i.e., hPMS2-134, which carries a truncating mutation at codon 134; the specification further indicates that other dominant negative mutants can be identified from cells of different species organisms, such as humans, animals, yeast, or bacteria, by screening the cells for defective mismatch repair or that such mutants can be artificially created by producing variants of hPMS2-134 (p. 9, lines 13-19, p. 10, lines 1-5). The art does not teach dominant negative pMS2 mutants other than hPMS2-134. Therefore, with the exception of hPMS2-134, Applicant did not provide specific materials with which the invention could be practiced. The art does not provide such

materials. Applicant argues that Example 1, 3, and 4 of the specification teach assessing defective mismatch repair in a given cell, and that by using the guidance provided by these example, one of skill in the art would be able to identify dominant negative PMS2 mutant by routine experimentation. Example 1 teaches that stable fibroblasts genetically engineered to express hPMS2-134 generate β-galactosidase due to a frame-restoring mutation (i.e., are defective in mismatch repair); the result was expected because hPMS2-134 was described in the prior art as being a dominant negative mutant. Examples 3 and 4 provide prophetic screening strategies for identifying clones expressing highly antigenic polypeptides using the genetically engineered cells disclosed in Example 1. It is noted that all methods use a stable cell transfected with vector encoding a well-known dominant negative mutant (i.e., hPMS2-134) and none teaches how to identify a dominant negative variant of PMS2. Screening for mutated antigens is distinct from identifying a dominant negative PMS2. Therefore, the specification does not provide any guidance as to how identify dominant negative PMS2 in a given cell. Even if, for the sake of the argument, one of skill in the art would be able to identify a cell defective in mismatch repair, the specification does not provide any guidance as to how specifically identify dominant negative PMS2 in that cell. It is noted that mismatch repair requires the activity of various genes that interact with each other in a complex way (see also the non-final Office action of 12/18/2006). When a cell is defective in mismatch repair, the defect can be in any of these genes or in a combination of genes. The specification does not provide any guidance of how to discern the defects in PMS2 from the defects in the other genes. Identifying dominant

negative mutants of any mismatch repair gene, including PMS2, is not routine in the art and, without sufficient guidance to a specific method, one of skill in the art would require undue experimentation to find a dominant negative mutant, as claimed. For these reasons, and for the reasons set forth in the non-final Office action mailed on 12/18/2006, the rejection is maintained.

It is noted that claims 74 and 75 are directly or indirectly dependent from the rejected claims 70, 72, and 73.

Claim Rejections - 35 USC § 102

7. The rejections of claims 70, 73-75, and 77 under 35 U.S.C. 102(b) as being anticipated by Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641) and of claims 70 and 73-77 under 35 U.S.C. 102(e) as being anticipated by Nicolaides et al. (U.S. Patent No. 6,146,894) are withdrawn in response to Applicant's amendments to the claims to recite selecting cells comprising a mutation that results in enhanced immunogencity of the preselected immunogen. The amendments were filed on 03/19/2007. However, similar rejections are made below citing prior art evidencing that mutations can result in enhanced antigen immunogenicity.

Claim Rejections - 35 USC § 103

8. The rejections of claims 70 and 72-77 under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641), in view of Nicolaides et al. (U.S. Patent 6,825,038) and of claims 70 and 73-77 as being

unpatentable over Nicolaides et al. (U.S. Patent No. 6,146,894), in view of Nicolaides et al. (U.S. Patent 6,825,038) are withdrawn in response to Applicant's amendments to the claims to recite selecting cells comprising a mutation that results in enhanced immunogencity of the preselected immunogen. The amendments were filed on 03/19/2007. However, similar rejections are made below citing prior art evidencing that mutations can result in enhanced antigen immunogenicity.

New Rejections

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 70 and 73-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-13 and 16-18 of U.S. Patent No. 6,146,894, in view of Parkhurst et al. (J Immunol, 1996, 157: 2539-2548). Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a dominant negative allele of a PMS2 gene, selecting the cells comprising a mutation in the preselected immunogen that results in enhanced antigenicity, and expressing the polynucleotide sequence encoding the preselected immunogen in a genetically stable cell and to a homogeneous culture of cells produced by this method (claims 70 and 77). The PMS2 gene is the human PMS2 (claim 73), the allele comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76).

The patent claims are drawn to: **(i)** a method of generating a mutation in a gene of interest (i.e., a preselected immunogen) by growing a population of mammalian cells expressing the gene of interest and a dominant negative allele of aPMS2 gene, wherein the dominant negative allele is a truncated human PMS2 (i.e., *in vitro* introduction, into the cell expressing a preselected immunogen, of a dominant negative allele of a PMS2 gene) and identifying a cell in which the preseleced immunogen is mutated (i.e.,

selecting the cell), wherein the cell is hypermutable (i.e., a method of generating a hypermutated preselected immunogen) (claims 11 and 16-18). Identifying/selection is by analyzing the sequence of the gene of interest or of the mRNA transcribed from the gene of interest (claims 12 and 13), i.e., determining whether the polynucleotide comprises a mutation as compared to the wild type, and **(ii)** a homogenous composition of cultured hypermutable, mammalian cells comprising a dominant negative allele of PMS2 (claim 7), wherein the dominant negative allele of PMS2 is human PMS2 (claim 8) comprising the first 133 amino acids of the human PMS2 (claims 9 and 10). The specification defines that the dominant negative allele of the human PMS2 is hPMS2-134 comprising codons 1-134 of the wild type hPMS2 (column 3, lines 27-32, Example 1), and therefore it is the same as the claimed truncated human PMS2 mutant, i.e., it has a truncation mutation at codon 134, wherein the truncation mutations is a thymidine at position 424 of the wild type hPMS2. It is noted that, since the claimed hPMS2-134 consists of codons 1-134 of the wild type hPMS2 it comprises the first 133 amino acids of the wild type hPMS2. With respect to the limitation of the cell being genetically stable, the mammalian cell of the patent is genetically stable enough once it acquires the mutation in the preselected gene since it is possible to detect this mutation. In alternative, it would have been obvious to one of skill in the art, at the time the invention was made, to restore the genetic stability of the mammalian cell once the desired mutation was obtained, by suppressing the activity of the dominant negative PMS2, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain continuous expression of preselected genes comprising the

desired mutations. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the identifying/selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. Thus, the patented claims 7-13 and 16-18 anticipate claims 70 and 73-77 of the instant application. Since the claims of the U. S. Patent No. 6,146,894 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

11. Claims 70 and 72-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-7, and 12 of U.S. Patent No. 6,808,894, in view of Parkhurst et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a dominant negative allele of a PMS2 gene, selecting the cells comprising a mutation in the preselected immunogen that results in enhanced antigenicity, and expressing the polynucleotide sequence encoding the preselected

immunogen in a genetically stable cell and to a homogeneous culture of cells produced by this method (claims 70 and 77). The PMS2 gene is the human PMS2 (claim 73), the allele comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76). Introduction of the polynucleotide comprising the dominant negative truncated PMS2 mutant into the cell expressing the preselected immunogen can take place in the presence of a DNA mutagen (claim 72).

The patent claims recite: **(i)** a method for making a hypermutable antibody-producing cell *in vitro* by co-introducing into a cell an immunoglobulin gene (i.e., a preselected therapeutic immunogen) and dominant negative human PMS2 (claims 1, 3, and 6). The dominant negative human PMS2 has a truncation mutation at codon 134 (claim 4), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 5) and the method further comprises restoring genetic stability to the hypermutable cell (claim 12). Thus, the patent claims are drawn to a method of making a genetically stable cell expressing a hypermutated immunogen, i.e., expressing a polynucleotide encoding the preselected immunogen into a genetically stable cell, and **(ii)** a homogenous culture of isolated hypermutable mammalian cells wherein the cell produce antibodies and express a dominant negative truncated PMS2 mutant (claim 7). The specification discloses that DNA mutagens can be used to enhance the mutation rate (column 8, lines 1-10). With respect to the limitation of selecting cell comprising a mutation in the gene encoding the preselected immunogen based on analyzing the

gene for the presence of said mutation as compared to the wild type, this is not innovative over the prior art. It would have been obvious to one of skill in the art to do so and one of skill in the art would have expected a reasonable expectation of success in doing such. One of skill in the art would have been motivated to do so in order to selected for cells expressing the desired mutations, for example mutations resulting in immunoglobulins with higher affinity for the antigen as compared to the wild type immunoglobulins. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the identifying/selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. Thus, the patented claims 1, 3-7, and 12 anticipate claims 70 and 72-77 of the instant application. Since the claims of the U. S. Patent No. 6,808,894 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

12. Claims 70 and 72-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 6 of U.S. Patent No.

6,825,038, in view of Parkhurst et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a dominant negative allele of a PMS2 gene, selecting the cells comprising a mutation in the preselected immunogen that results in enhanced antigenicity, and expressing the polynucleotide sequence encoding the preselected immunogen in a genetically stable cell and to a homogeneous culture of cells produced by this method (claims 70 and 77). The PMS2 gene is the human PMS2 (claim 73), the allele comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76). Introduction of the polynucleotide comprising the dominant negative truncated PMS2 mutant into the cell expressing the preselected immunogen can take place in the presence of a DNA mutagen (claim 72).

The patent claims recite an *in vitro* method for generating a mutation in a gene of interest in a hypermutable cell (i.e., generating a hypermutated immunogen) by introducing into the hypermutable cell expressing the gene of interest a dominant negative PMS2 allele under the control of an inducible promoter, testing the cell for a mutation in the gene of interest, and stabilizing the genome of the cell expressing the mutated gene of interest by decreasing the activity of the dominant negative allele (claims 1 and 6), i.e., selecting cells comprising a mutation in the gene of interest.

Testing comprises analyzing the nucleotide sequence of the gene of interest (claim 2) or the mRNA transcribed from the gene of interest (claim 3). With respect to the limitation of compare these sequences to the wild type, this is a requirement for the testing method. The specification discloses that DNA mutagens can be used to enhance the mutation rate (column 2, lines 61-65) and that the dominant negative PMS2 allele is hPMS2-134 (column 5, lines 1-67, Examples 1 and 2), i.e., it is the same as the claimed truncated human PMS2 mutant and therefore, it has a truncation mutation at codon 134, wherein the truncation mutations is a thymidine at position 424 of the wild type hPMS2. With respect to the limitation recited by the instant claim 77, one of skill in the art would have been motivated to obtain a homogenous population of cells expressing a mutated gene of interest in order to constantly produce this gene. Although the application claims do not recite controlling hPMS2-134 expression by an inducible promoter, one of skill in the art would have been motivated to modify the claimed invention and use such because inactivating hPMS2-134 would be easily achieved when needed, without additional manipulations. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the identifying/selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. Thus, the patented

claims 1-3 and 6 anticipate claims 70 and 72-77 of the instant application. Since the claims of the U. S. Patent No. 6,825,038 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

13. Claims 70 and 72-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 8-10 of U.S. Patent No. 6,737,268, in view of Parkhurst et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a dominant negative allele of a PMS2 gene, selecting the cells comprising a mutation in the preselected immunogen that results in enhanced antigenicity, and expressing the polynucleotide sequence encoding the preselected immunogen in a genetically stable cell and to a homogeneous culture of cells produced by this method (claims 70 and 77). The PMS2 gene is the human PMS2 (claim 73), the allele comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76). Introduction of the polynucleotide comprising the dominant negative truncated PMS2 mutant into the cell expressing the preselected immunogen can take place in the presence of a DNA mutagen (claim 72).

The patent claims recite a method of making a therapeutically hypermutated immunogen by introducing into a cell expressing a preselected immunogen *in vitro* a dominant negative allele of a PMS2 gene, selecting cells that comprise a mutation, wherein the genetic stability of the selected cells is restored and a homogenous culture of selected and stable cells is produced (claims 1 and 8-10), wherein the dominant negative allele of a PMS2 gene is the human PMS2 comprising a truncation mutation at codon 134 (claims 2 and 3), wherein the truncation mutation is thymidine at nucleotide 424 of the wild type PMS2 (claim 4), and wherein the introduction of the polynucleotide comprising the dominant negative truncated PMS2 mutant into the cell expressing the preselected immunogen can take place in the presence of a DNA mutagen (claim 8). With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. Thus, the patented claims 1-4 and 8-10 anticipate claims 70 and 72-77 of the instant application. Since the claims of the U. S. Patent No. 6,737,268 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 70, 73-75, and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641, of record), as evidenced by Parkhurst et al.

** The instant rejection is based on the interpretation that the genetically stable cell is the cell comprising the truncated dominant negative PMS2, wherein the stability of the cell was restored.

The teachings of Nicolaides et al. are applied as set forth in the non-final Office action of 12/18/2006. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method of Nicolaides et al. generates random mutations and that a number of mutations would result in increased antigenicity of β-galactosidase; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the selecting step would necessarily render cells expressing

β-galactosidase with enhanced antigenicity. Since Nicolaides et al. teach all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art.

16. Claims 70 and 73-77 are rejected under 35 U.S.C. 102(e) as being anticipated by Nicolaides et al. (U.S. Patent No. 6,146,894, of record), as evidenced by Parkhurst et al.

** The instant rejection is based on the interpretation that the genetically stable cell is the cell comprising the truncated dominant negative PMS2, wherein the stability of the cell was restored.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The teachings of Nicolaides et al. are applied as set forth in the non-final Office action of 12/18/2006. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method of Nicolaides et al. generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547,

column 1, first full paragraph). Therefore, the selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. Since Nicolaides et al. teach all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 70 and 72-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641), in view of both Nicolaides et al. (U.S. Patent 6,825,038, of record) and Parkhurst et al.

** The instant rejection is based on the interpretation that the genetically stable cell is the cell comprising the truncated dominant negative PMS2, wherein the stability of the cell was restored.

The teachings of Nicolaides et al. (Mol Cell Biol) and Nicolaides et al. (U.S. Patent 6,825,038) are applied as set forth in the non-final Office action of 12/18/2006. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method of Nicolaides et al. generates random mutations and that a number of mutations would result in increased antigenicity of β-galactosidase; the prior art teaches mutations in the

wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

19. Claims 70 and 73-77 are rejected under 35 U.S.C. 102(e) as being unpatentable over Nicolaides et al. (U.S. Patent No. 6,146,894), in view of both Nicolaides et al. (U.S. Patent 6,825,038) and Parkhurst et al.

** The instant rejection is based on the interpretation that the genetically stable cell is the cell comprising the truncated dominant negative PMS2, wherein the stability of the cell was restored.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the

application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The teachings of Nicolaides et al. (U.S. Patent No. 6,146,894) and Nicolaides et al. (U.S. Patent 6,825,038) are applied as set forth in the non-final Office action of 12/18/2006. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method of Nicolaides et al. generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. Thus, the claimed invention was *prima facie* obvious at the time the invention was made

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

Joe Woitach
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